RESEARCH PAPER

A Hybrid Continuous-Discrete Mathematical Framework for Modeling Adverse Drug Reaction Accumulation and Early Signal Detection in Pharmacovigilance

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ABSTRACT

Background: Spontaneous adverse drug reaction (ADR) reporting systems produce observations at discrete reporting intervals, while reporting intensity may change continuously. Cumulative report counts are difficult to interpret because reporting volume can be influenced by utilization, stimulated reporting, regulatory actions and changes in reporting practice.

Objective: To formulate a hybrid continuous-discrete mathematical framework for describing ADR report accumulation and define a candidate residual-based early-warning procedure for computational evaluation.

Methods: Let C(t) denote expected cumulative reports and λ(t) the reporting intensity. The continuous component is defined by $dC/dt = \lambda(t)$ and $d\lambda/dt = r\lambda(t)\,[1 - \lambda(t)/K]$, with $r > 0$ and $K > 0$. Interval counts are represented as $Y_k \sim \text{Poisson}(\mu_k)$, where μ_k is the integral of λ(t) over the reporting interval. A discrete conditional-mean recurrence, $\mu^D_{k+1} = \omega + \varphi Y_k + \psi\mu^D_k$, is combined with the continuous forecast through a convex weighting parameter α. We propose an exploratory warning statistic, a standardized forecast residual. Planned analyzes include mathematical analysis, synthetic-data simulation, sensitivity analysis and comparative forecasting.

Expected contribution: The framework provides a formal link between continuous reporting dynamics and discrete count observations. Proof-of-concept simulations compare forecast error and exploratory warning behavior in four simulated scenarios. The findings are preliminary and simulation-specific, validation on real-world pharmacovigilance data and calibration of alert thresholds still are required. The framework is meant to be a supplemental monitoring strategy and cannot in itself establish causality or comparative drug safety.

Keywords: Adverse drug reactions; Pharmacovigilance; Hybrid modelling; Ordinary differential equations; Forecasting; Early-warning systems.

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1. INTRODUCTION

Spontaneous reporting systems are important sources of post-marketing information on suspected adverse pharmaceutical events. Quantitative methods, such as the proportional reporting ratio (PRR), reporting odds ratio (ROR), information component and empirical Bayes approaches, are utilized to rank drug-event pairs for review. These approaches give helpful screening evidence, but they have various assumptions and are subject to under-reporting, stimulated reporting, confounding and variances in reporting methodology. A statistical signal is a signal to be assessed, not evidence that a treatment caused an event.[1-8]

Another question involves the time evolution of the counts of reports. Reports are observed at distinct time points, while the fundamental process of report creation and accumulation occurs in the time between those observation points. A model linking continuous time intensity to discrete observations can help to separate anticipated temporal variation from exceptional big deviations. Related research on count monitoring has used Poisson and negative-binomial models to detect shifts in surveillance series, offering a methodological basis for evaluating warning criteria based on residuals.[9-12]

In the present study, we propose a hybrid continuous-discrete framework and validate it on reproducible synthetic simulations. The contribution is a formal model

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specification and visible proof-of-concept comparison. It is not claimed that the framework is clinically validated or superior under all reporting scenarios.

1.1 Aim and Objectives

The aim is to formulate a hybrid model of cumulative ADR report accumulation and investigate its suitability for exploratory early-warning monitoring.

- Define a continuous-time reporting-intensity model and connect it to interval-level count observations.
- Specify a discrete conditional-mean model and a transparent hybrid forecasting rule.
- Identify mathematical properties and parameter constraints needed for coherent predictions.
- Design simulations to compare forecasting error and warning behavior across stable, increasing, saturating and abrupt-change scenarios.
- Set out requirements for later evaluation using real-world pharmacovigilance data.

2. MATERIALS AND METHODS

2.1 Study design and current status

This is a mathematical model-development study. A reproducible proof-of-concept simulation has been completed using synthetic Poisson counts under four prespecified reporting scenarios. No pharmacovigilance dataset was analyzed. Numerical results are reported in Section 3 and should be interpreted as simulation findings, not empirical estimates of drug safety.

2.2 Notation and observation model

Let $t \geq 0$ denote continuous time and $0 = t_0 < t_1 < \ldots < t_n$ be observation times. Let $C(t)$ be the expected cumulative number of reports by time t and $\lambda(t) \geq 0$ the instantaneous reporting intensity. The observed cumulative count at t_k is N_k, and the new count during interval k is $Y_k = N_k - N_{k-1}$. Thus $N_k = N_0 + \Sigma_{j=1}^{k} Y_j$, and Y_k must be non-negative. [13]

$$Y_k \mid \lambda(\cdot) \sim \text{Poisson}(\mu_k), \ \mu_k = \int_{t_{k-1}}^{t_k} \lambda(s)\, ds. \quad (1)$$

The Poisson assumption is a baseline rather than a guaranteed description of spontaneous reports. Overdispersion, temporal dependence and reporting delays may require a negative-binomial or other count model in subsequent sensitivity analyses. [14]

2.3 Continuous-time component

The continuous component is defined by the coupled differential equations:

$$dC(t)/dt = \lambda(t), \ d\lambda(t)/dt = r\,\lambda(t)\,[1 - \lambda(t)/K]. \quad (2)$$

Here $r > 0$ is a growth-rate parameter and $K > 0$ is a saturation level for reporting intensity. Given $\lambda(0) = \lambda_0$ with $0 < \lambda_0 < K$ and $C(0) = C_0$, the logistic intensity solution is

$$\lambda(t) = K / \{1 + A \exp(-rt)\}, \ A = K/\lambda_0 - 1. \quad (3)$$

Integrating $\lambda(t)$ gives the expected cumulative trajectory:

$$C(t) = C_0 + (K/r) \ln[(\exp(rt) + A)/(1 + A)]. \quad (4)$$

Under these parameter constraints, $\lambda(t)$ remains positive and approaches K; $C(t)$ is non-decreasing. Since intensity approaches a positive constant, cumulative reports continue to grow approximately linearly at long times. This is a candidate representation of saturation in reporting intensity, not a claim that all ADR series follow logistic dynamics. [15]

2.4 Discrete-time component

To represent serial dependence in interval counts, the proposed discrete conditional mean is

$$\mu^{D}_{k+1} = \omega + \varphi Y_k + \psi \mu^{D}_k, \ \omega > 0, \ \varphi \geq 0, \ \psi \geq 0. \quad (5)$$

The count observation may be represented as $Y_{k+1} \mid \mathcal{F}_k \sim \text{Poisson}(\mu^{D}_{k+1})$, where $\mathcal{F}_k$ contains information available through interval k. This is a candidate count-forecasting component. Parameter estimation, identifiability and residual diagnostics must be examined before it is used for inference or warning decisions. [13,14]

2.5 Hybrid forecast

Let $\hat{\mu}^{C}_{k+1}$ be the continuous-model expected count for the next interval, calculated by integrating the fitted intensity over $[t, t_{k+1}]$, and let μ^{D}_{k+1} be the discrete-model forecast. The hybrid forecast is

$$\mu^{H}_{k+1} = \alpha\, \hat{\mu}^{C}_{k+1} + (1 - \alpha)\, \mu^{D}_{k+1}, \ 0 \leq \alpha \leq 1. \quad (6)$$

The weight α determines the relative contribution of the two forecasts. It should be selected using training data or rolling-origin validation confined to the training period, not on the final test period. For both forecasts, they must be non-negative and expressed for the same observation interval before being combined. [16]

2.6 Exploratory early-warning statistic

A one-step standardized residual can be defined as

$$Z_k = (Y_k - \mu^{H}_k) / \sqrt{\max(\mu^{H}_k, \varepsilon)}, \ \varepsilon > 0. \quad (7)$$

A candidate warning is generated when Z_k exceeds a prespecified upper threshold h. The small constant ε prevents division by zero when the forecast mean is zero or close to zero. Because the residual distribution may not be standard normal under fitted parameters, serial dependence or overdispersion, h must be calibrated empirically using simulation or an appropriate predictive distribution. A single exceedance is an exploratory flag, not a validated safety signal. False-alarm rates and warning delays must be evaluated explicitly. [17,18]

2.7 Computational evaluation

Synthetic series were generated under four conditions: (i) stable baseline reporting; (ii) gradual increase in intensity; (iii) saturation in intensity; and (iv) an abrupt increase introduced at a known time. Forecast comparisons used 100 replicates per scenario and warning analyses used 200 replicates per scenario. Overdispersion, sparse counts, seasonality, changing observation intervals and parameter misspecification remain important extensions for future work. [10-12]

The continuous-only, discrete-only and hybrid forecasts were compared on identical training, validation and test windows. Mean absolute error (MAE) and root mean squared error (RMSE) were used to present a predicted error over replicates. Warning behavior was assessed using the exploratory standardized-residual threshold $Z_t > 3$, with alert counts summarized for the stable, gradual-increase and saturating scenarios and pre-change false alarms, five-interval detection and detection delay assessed for the abrupt-change scenario. The evaluation is a proof of concept; threshold calibration, over dispersed data and additional baseline methods remain for future work.

2.8 Mathematical checks

The study should confirm intensity and predictions for positivity, cumulative path for monotonicity, numerical convergence for step-size refinement and parameter sensitivity and stability of the discrete recurrence. The condition $\varphi + \psi < 1$ can be studied as a restriction for stability of the mean recurrence in simple cases, but its adequacy should be justified for the precise stochastic specification, not assumed as a general theorem. Parameter estimate should contain uncertainty, and checks for practical identifiability. [13,14]

3. RESULTS

3.1 Simulation design

A reproducible proof-of-concept simulation was performed using synthetic Poisson count series only; no real-world pharmacovigilance data were analyzed. Four scenarios were simulated over 120 intervals: (i) stable intensity $\lambda_t = 15$; (ii) gradual increase $\lambda_t = 8 \exp(0.015t)$; (iii) saturating intensity $\lambda_t = 30/ [1 + \exp \{-0.07(t - 45)\}]$; and (iv) an abrupt increase from $\lambda_t = 10$ to $\lambda_t = 25$ at $t = 85$. Forecast comparisons used 100 independently generated series per scenario. Models were fitted to intervals 0-69; the hybrid weight α was selected from 21 equally spaced values between 0 and 1 using validation intervals 70-79. Forecast errors were evaluated on intervals 90-119 using one-step-ahead predictions. For the discrete forecast, the observed count from the immediately preceding interval was available, as it would be in rolling one-step monitoring.

For the continuous component, constant, exponential and logistic intensity candidates were fitted by Poisson likelihood and selected using Akaike's information criterion (AIC) on the training data. The discrete component used a non-negative linear conditional mean, $\mu^D_t = a + bY_{t-1}$, fitted by constrained least squares. The hybrid forecast was $\mu^H_t = \alpha\mu^C_t + (1 - \alpha)\ \mu^D_t$. Forecast performance was summarized using mean absolute error (MAE) and root mean squared error (RMSE). A separate warning experiment used 200 series per scenario and the exploratory standardized residual threshold $Z_t > 3$. For the abrupt-increase scenario, pre-change false alarms were counted over $t = 70–84$ and detection were defined as at least one warning during $t = 85$-89. Seeds were fixed at 314159 for forecasting and 271828 for warning analysis. [19]

3.2 Forecasting performance

Table 1 reports the mean (standard deviation) of MAE and RMSE across 100 synthetic replicates per scenario. Lower values indicate smaller forecast errors under the specified simulation design.

Scenario	Model	MAE, mean (SD)	RMSE, mean (SD)
Stable	Continuous	3.33 (0.64)	4.10 (0.71)
Stable	Discrete	3.15 (0.43)	3.89 (0.52)
Stable	Hybrid	3.23 (0.52)	3.97 (0.59)
Gradual increase	Continuous	7.42 (4.07)	8.79 (4.24)
Gradual increase	Discrete	11.55 (1.98)	13.41 (1.93)
Gradual increase	Hybrid	7.11 (4.05)	8.49 (4.21)
Saturating	Continuous	5.25 (1.94)	6.38 (1.97)
Saturating	Discrete	6.06 (0.90)	7.53 (1.13)
Saturating	Hybrid	4.91 (0.96)	6.08 (1.11)
Abrupt increase	Continuous	15.00 (1.46)	15.81 (1.45)
Abrupt increase	Discrete	14.40 (1.29)	15.26 (1.28)
Abrupt increase	Hybrid	14.61 (1.24)	15.46 (1.24)

Across the stable scenario, the discrete model had the lowest average error, while the hybrid model was intermediate. In the gradual-increase scenario, the hybrid model had the lowest average MAE and RMSE, although its results were close to the continuous model and variability across replicates was substantial. In the saturating scenario, the hybrid model had the lowest average errors. In the abrupt-increase scenario, the minimum average errors were obtained using the discrete model between the discrete and the continuous model's hybrid model. So, the hybrid forecast was not better in all cases but dependent on the data-generating method.

The mean selected α values were 0.537 for stable reporting, 0.891 for gradual increase, 0.851 for saturating reporting and 0.409 for abrupt increase. In the training samples, AIC selected a constant intensity in 79/100 stable replicates, an exponential intensity in 88/100 gradual-increase replicates, a logistic intensity in 100/100 saturating replicates, and a constant intensity in 86/100 abrupt-increase replicates. These are properties of the prespecified synthetic scenarios and fitting procedure, not evidence about real ADR databases.

3.3 Exploratory warning behavior

Table 2 summarizes the exploratory threshold rule $Z_t > 3$ across 200 replicates per scenario. For the first three scenarios, the number of alerts is reported per 50 monitored intervals. For the abrupt-increase scenario, false alarms are counted before the change (t = 70-84), and detection is the proportion of replicates with at least one alert during the first five intervals after the change (t = 85-89).

Scenario	Model	Mean alerts / 50 periods or pre-change false alarms	Detected within 5 intervals
Stable	Continuous	0.285 alerts / 50	-
Stable	Discrete	0.220 alerts / 50	-
Stable	Hybrid	0.205 alerts / 50	-
Gradual increase	Continuous	2.185 alerts / 50	-
Gradual increase	Discrete	11.200 alerts / 50	-
Gradual increase	Hybrid	2.175 alerts / 50	-
Saturating	Continuous	0.435 alerts / 50	-
Saturating	Discrete	2.595 alerts / 50	-
Saturating	Hybrid	0.450 alerts / 50	-
Abrupt increase	Continuous	0.090 false alarms (pre-change)	100.0%
Abrupt increase	Discrete	0.100 false alarms (pre-change)	100.0%
Abrupt increase	Hybrid	0.080 false alarms (pre-change)	100.0%

In the abrupt-increase scenario, all three techniques gave at least one warning in five intervals in all 200 repeats; the mean detection delay across detected replicates was 0.145 intervals for the continuous model, 0.130 for the discrete model and 0.145 for the hybrid model. On this particular arrangement, the pre-change false alarms were few on average. The change from 10 to 25 reports each interval, however, was intentionally big, the threshold was exploratory, and the simulation did not calibrate a target false-alarm probability. Hence, these data show behavior under a large synthetic alteration, not confirmed detecting performance early.

3.4 Summary of computational findings

The simulations demonstrate that the hybrid forecast is competitive and achieved the lowest average error in the gradual and saturated scenarios, but it was not the best in the stable or abrupt-change scenarios. The discrete residual rule produced more warnings during steady increase than the continuous or hybrid rules, indicating that the threshold statistic can be sensitive to model misspecification or trend change as well as abrupt anomalies. These results are a call for further methodological review, not a claim of general superiority. Confidence intervals, wider scenario grids, different count distributions and comparison with established control-chart baselines are still required.

Figures 1-4 summarize example fitted trajectories, aggregate forecast errors, warning-alert burden and selected hybrid weights.

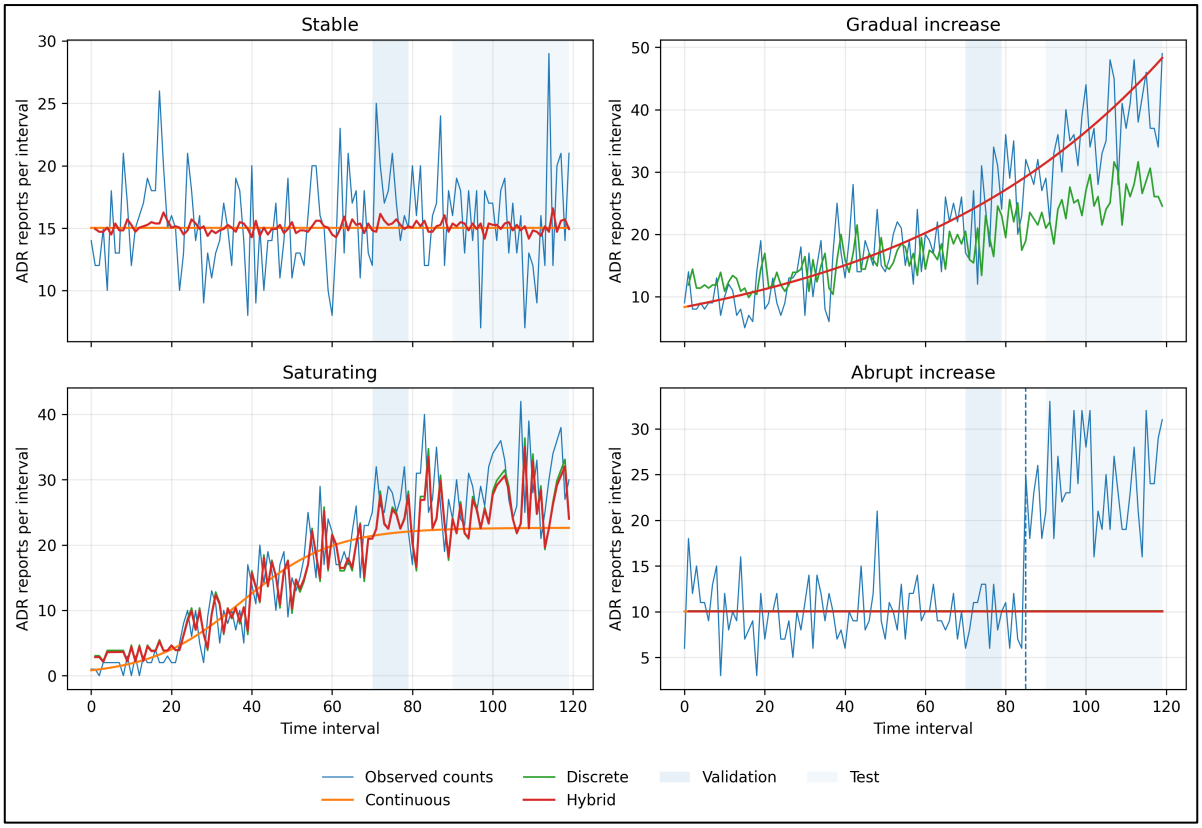


Figure 1. Representative synthetic ADR count trajectories and One-step-ahead forecasts and sample synthetic ADR-count trajectories from continuous, discrete, and hybrid models in four simulated scenarios. Dashed lines indicate sudden change points; shaded regions represent validation and test periods.

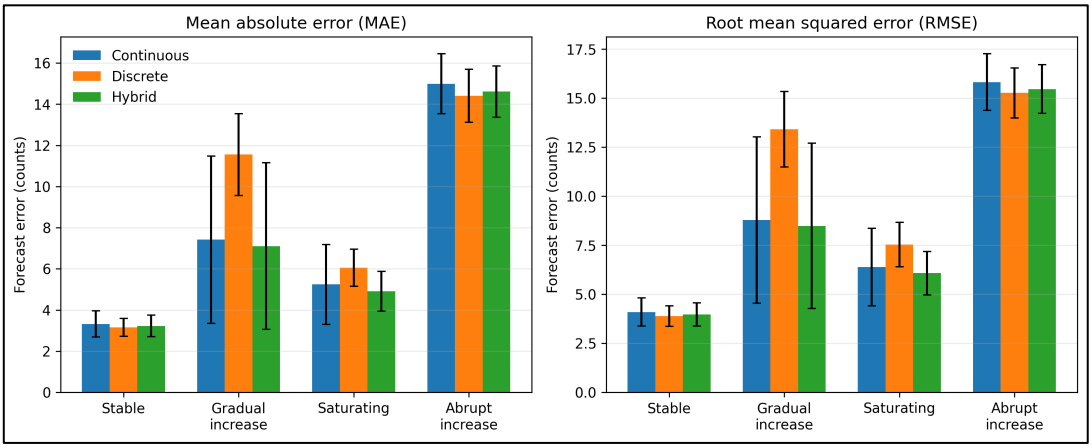


Figure 2. Predict scenario performance throughout 100 simulation repeats. Mean MAE and RMSE are shown; error bars are one standard deviation. Better prediction accuracy with lower values.

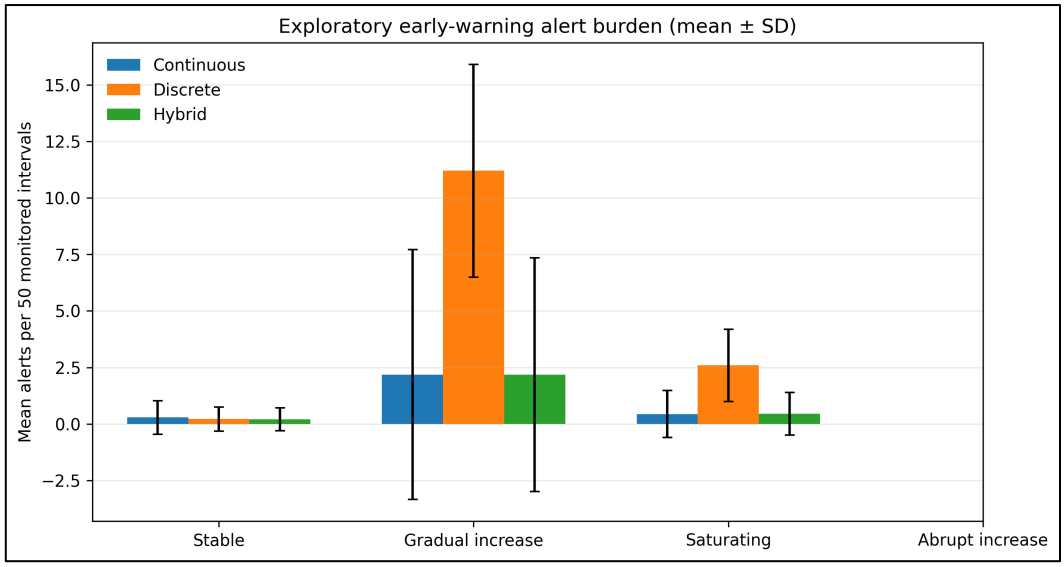


Figure 3. Early-warning alert burden exploration across 200 scenario simulation repetitions. Bars reflect the mean alerts per 50 monitored intervals; error bars are one standard deviation. Standardized residual larger than 3 was the criteria.

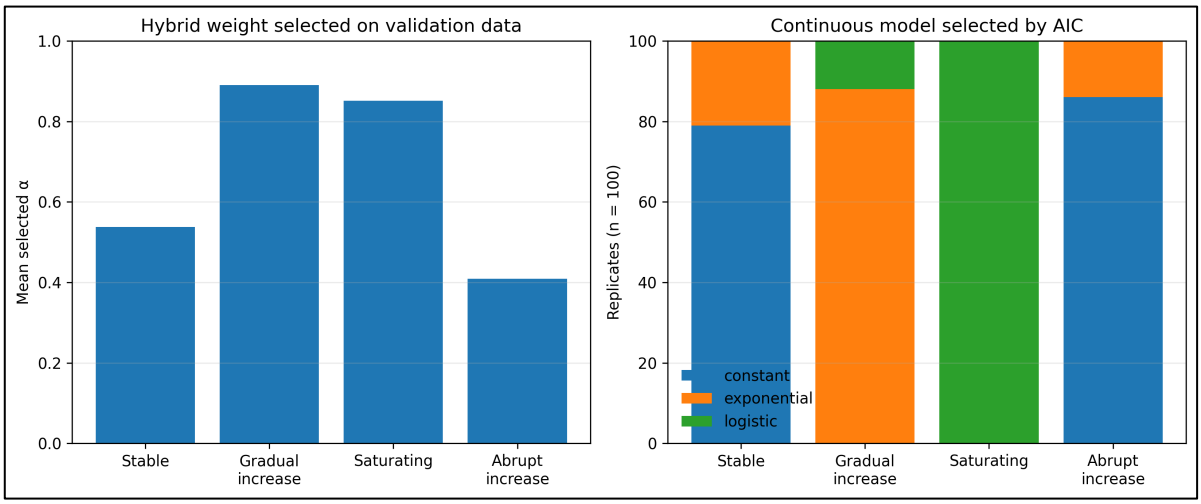


Figure 4. Mean hybrid weight (α) selected on validation data and AIC-based selection frequencies for the continuous intensity model across 100 forecast replicates per scenario.

4. DISCUSSION

The system mixes continuous and discrete projections from a continuous intensity process with discrete count data. Its benefit is conceptual. The continuous section encodes a smooth trajectory, whereas the discrete part adapts to recent interval counts. Whether this combination improves prediction is empirical, not mathematical. [20,21]

The framework also varies from past disproportionality techniques in the immediate target. The suggested model focuses on temporal fluctuations in report counts, while PRR, ROR and related measures analyze disproportional reporting of a drug-event pair in a reporting database. These goals complement each other. Changes in exposure, reporting behavior, media interest, regulatory communications, or database operations may increase reports, not a new drug issue. Thus, every warning should prompt clinical and epidemiological evaluation, not causality. [6-8,10,11,22]

4.1 Limitations

Restrictions are likely not studying real-world data, external validity and practical utility are uncertain. Second, the logistic intensity model may overlook seasonality, multiple changes and extended reporting delays. Third, Poisson data may underestimate variation. Fourth, without training/validation, hybrid weighting and warning levels overfit. Fifth, cumulative counts are construction-dependent; model fitting should utilize interval increments or a likelihood that accounts here. Under- and stimulated reporting often affect spontaneous reports, which often lack a denominator. [7,8,23,24]

4.2 Future Scope

Simulation studies should incorporate over distributed and sparse counts, seasonality, delayed reports, many modifications, model misspecification, and warning threshold calibration against prespecified false-alarm targets. The framework should then be evaluated on a real pharmacovigilance time series with documented extraction

dates, inclusion criteria, drug/event definitions, deduplication strategy and reporting intervals. Comparison with established count-monitoring baselines and appropriate pharmacovigilance signal-detection methods is required before practical claims are made. [9,11,12,21,25]

5. CONCLUSIONS

A candidate hybrid continuous-discrete framework has been specified for modelling ADR report accumulation and exploring residual-based early warning. Proof-of-concept simulations show that forecast performance varies by scenario: the hybrid forecast had the lowest mean error in the gradual and saturating scenarios but was not best in the stable or abrupt-change scenarios. These synthetic findings support further methodological evaluation only. Real-world validation, threshold calibration, overdispersion checks and independent replication are required before operational use.

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CONFLICT OF INTEREST

To be completed by the author(s) with an accurate declaration.

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